

IN THE CLAIMS

1. (Original) A modified adenovirus fiber, comprising a modification to the fiber protein shaft, wherein the modification comprises a modification selected from among:

- a modification of a last full repeat;
- a modification of a β-repeat corresponding to a third β-repeat and
- a modification of a last full repeat; and
- a modification of one or both of a modification of a last full repeat and a modification of at least one amino acid in a contiguous sequence of amino acids corresponding to the amino acid sequence TTVT/S set forth in SEQID No. 44 in a third β-repeat, whereby binding of the fiber or of a viral particle containing such fiber to the Coxsackie-Adenovirus Receptor (CAR) is reduced compared to the unmodified fiber.

2. (Original) A modified adenovirus fiber, comprising a modification to the fiber protein shaft, whereby binding of the modified fiber to Coxsackie- Adenovirus Receptor (CAR) is reduced or eliminated, wherein: the unmodified fiber binds the Coxsackie-Adenovirus Receptor (CAR); and the modification comprises a modification of a repeat corresponding to the last full β-repeat, or the third β-repeat and the last full β-repeat of the shaft or one or both of the last full β-repeat and a portion of the third, β-repeat that comprises the TTVT/S motif (SEQID No. 44) or a corresponding motif.

3. (Currently Amended) A modified fiber of Claim 1 [[or 2]], wherein the modified fiber binds to CAR with less than 50%, 40%, 30%, 20%, 10%, 5%, 1 % of the binding affinity of the unmodified fiber.

4. (Currently Amended) A modified adenovirus fiber of ~~any of claims 1-3~~

Claim 1, wherein the modified fiber is more rigid than the unmodified fiber.

5. (Currently Amended) A modified adenovirus fiber of ~~any of claims 1-4~~

Claim 1, wherein the modification is a mutation, deletion, insertion or replacement of at least one amino acid in the fiber shaft repeat corresponding to the third repeat.

6. (Currently Amended) The modified adenovirus fiber of ~~any of claims 1-5~~

Claim 1, wherein the unmodified fiber is a fiber of a serotype C adenovirus.

7. (Original) The modified adenovirus fiber of Claim 6, wherein the serotype C adenovirus is Ad2 or Ad5.

8-9. (Cancelled).

10. (Currently Amended) The modified adenovirus fiber of ~~any of claims 1-6~~
Claim 1, wherein the third β-repeat is modified by replacing it with a corresponding repeat from a serotype D fiber shaft repeat sequence.

11. (Original) The modified adenovirus fiber of Claim 10, wherein the serotype D adenovirus is selected from the group consisting of Ad8, Ad9, Ad15, Ad19p and Ad37.

12. (Currently Amended) The modified adenovirus fiber of ~~any of claims 1-6~~
Claim 1, wherein the third β-repeat is modified by replacing it with a corresponding repeat selected from the group consisting of SEQ ID NOS: 58,66, 67 and 68.

13. (Currently Amended) The modified adenovirus fiber of ~~any of claims 1-12~~
Claim 1, wherein the modification is a mutation, deletion, insertion or replacement of at least one amino acid in a fiber shaft β-repeat corresponding to the last full β-repeat and/or corresponding to the third β-repeat.

14. (Original) The modified adenovirus fiber of Claim 13, wherein the unmodified fiber is a serotype C adenovirus fiber.

15. (Original) The modified adenovirus fiber of Claim 12, wherein the serotype C adenovirus is Ad2 or Ad5.

16. (Original) The modified adenovirus fiber of Claim 15, wherein the modification is a modification of at least one amino acid in a contiguous sequence of amino acids corresponding to those set forth in SEQ ID No. 46 or SEQ ID No. 47.

17. (Currently Amended) The modified adenovirus fiber of ~~any of claims 1-45~~ Claim 1, wherein the modification comprises replacement of the last full β -repeat with a corresponding repeat sequence from a serotype D adenovirus fiber shaft.

18. (Original) The modified adenovirus fiber of Claim 17, wherein the serotype D adenovirus is selected from the group consisting of Ad8, Ad9, Ad15, Ad19p and Ad37.

19. (Currently Amended) The modified adenovirus fiber of ~~any of claims 13-48~~ Claim 13, wherein the modification is in the last full repeat; and the last full repeat comprises a change of at least one amino acid in the repeat at contiguous amino acids corresponding to the amino acid sequence set forth in SEQID No. 49.

20. (Currently Amended) The modified adenovirus fiber of ~~any of claims 13-48~~ Claim 13, wherein the modification is in the last full repeat; and the last full repeat comprises a sequence of amino acids selected from the group consisting of SEQID NOS: 48, 59, 60 and 61.

21. (Currently Amended) The modified adenovirus fiber of ~~any of claims 1-7~~ Claim 1, wherein a contiguous sequence of amino acids corresponding to the third repeat of the fiber shaft is deleted.

22. (Currently Amended) The modified adenovirus fiber of ~~any of claims 1-7~~ Claim 1, wherein a contiguous sequence of amino acids corresponding to the last full repeat of the fiber shaft is deleted.

23. (Currently Amended) The modified adenovirus fiber of ~~any of claims 1-7~~

Claim 1, wherein a contiguous sequence of amino acids corresponding to the third repeat and the contiguous sequence of amino acids corresponding to the last full repeat are modified.

24. (Currently Amended) The modified adenovirus fiber of claim 22 or ~~claim 23~~, wherein the modification is a mutation, deletion, insertion or replacement of at least one amino acid in a fiber shaft repeat corresponding to the third repeat and/or the last full repeat.

25. (Original) The modified adenovirus fiber of Claim 24, wherein the unmodified fiber shaft is from a serotype C adenovirus.

26. (Original) The modified adenovirus fiber of Claim 25, wherein the serotype C adenovirus is Ad2 or Ad5.

27. (Original) The modified adenovirus fiber of Claim 25, wherein the modified repeats corresponding to the third repeat and the last full repeat are from a serotype D adenovirus.

28. (Original) The modified adenovirus fiber of Claim 27, wherein the serotype D adenovirus is selected from the group consisting of Ad8, Ad9, Ad 15, Ad19p and Ad37.

29. (Original) The modified adenovirus fiber of Claim 25, wherein the third repeat comprises a sequence selected from the group consisting of SEQ ID NOs. 58, 66, 67 and 68 and the last full repeat comprises an amino acid sequence selected from the group consisting of SEQ ID NOs. 48, 59, 60 and 61.

30. (Original) The modified adenovirus fiber of Claim 25, wherein the third repeat sequence is selected from a corresponding repeat sequence of a fiber protein from Ad8, Ad9, Ad 15, Ad19p or Ad37; and the last full repeat is selected from a

corresponding repeat sequence of a fiber protein from Ad8, Ad9, Ad15, Ad19p or Ad37.

31. (Currently Amended) The modified adenovirus fiber of ~~any of claims 1-30~~ Claim 1, wherein the modified adenovirus fiber further comprises at least one additional modification in the fiber protein, whereby the modified fiber binds to a receptor other than CAR with greater affinity than the unmodified fiber binds to such receptor.

32. (Currently Amended) The modified adenovirus fiber of ~~any of claims 1-30~~ Claim 1, wherein the modified adenovirus fiber further comprises at least one additional modification in the fiber protein; and the modification is a modification in the fiber knob that further reduces or eliminates any binding of the modified fiber to CAR.

33. (Original) The modified adenovirus fiber of Claim 31, wherein an additional modification is a modification of the Heparin Sulfate Proteoglycans (HSP) binding site in the fiber shaft.

34. (Currently Amended) The modified adenovirus fiber of ~~Claim 31 or claim~~ 32, wherein an additional modification is a modification in the fiber knob.

35. (Currently Amended) The modified fiber of ~~any of claims 1-34~~ Claim 1, wherein the fiber is shortened or its flexibility is reduced compared to the unmodified fiber.

36. (Original) The modified adenovirus fiber of Claim 34, wherein the fiber knob is replaced with fiber knobs from an adenovirus that does not interact with CAR.

37. (Original) The modified adenovirus fiber of Claim 36, wherein the adenovirus fiber knob that does not interact with CAR is Ad3 fiber knob, Ad41 short fiber knob, or Ad35 fiber knob.

38. (Original) The modified adenovirus fiber of Claim 34, wherein fiber knob mutations are mutations in the AB loop or CD loop.

39. (Original) The modified adenovirus fiber of claim 38, wherein fiber knob mutations are mutations in the AB loop or CD loop selected from K01 and K012.

40. (Original) A modified adenovirus fiber, comprising a fiber protein, wherein: the unmodified fiber binds the Coxsackie-Adenovirus Receptor (CAR); the fiber protein comprises a modification to the fiber protein shaft such that binding of the modified fiber to CAR is substantially reduced or eliminated ; the modified fiber comprises repeats corresponding to the third repeat and the last full repeat; and at least one repeat of the fiber shaft is deleted.

41. (Original) The modified adenovirus fiber of Claim 40, wherein the repeats corresponding to repeats 4-17 are deleted.

42. (Currently Amended) The modified adenovirus fiber of Claim 40 or ~~claim 41~~, wherein the fiber is from a serotype C adenovirus.

43. (Original) The modified adenovirus fiber of Claim 42, wherein the serotype C adenovirus is Ad2 or Ad5.

44. (Original) The modified adenovirus fiber of Claim 43, wherein the amino acids corresponding to positions 95-316 are deleted.

45. (Currently Amended) The modified adenovirus fiber ~~any of claims 1-39~~ Claim 1, wherein the fiber protein is from a serotype A, B, C or F adenovirus; and at least one amino acid corresponding to the consensus repeat sequence as set forth in

SEQ ID No. 49 is modified in the repeat corresponding to either the third repeat or the last full repeat.

46. (Currently Amended) A nucleic acid molecule, comprising a sequence of nucleotides that encodes a modified fiber of ~~any of claims 1-45~~ Claim 1.

47. (Original) The nucleic acid molecule of Claim 46 that comprises a vector.

48. (Currently Amended) The nucleic acid molecule of Claim 46 ~~or claim 47~~ that comprises heterologous nucleic acid encoding a gene product.

49. (Currently Amended) The nucleic acid molecule of ~~any of claims 46-48~~ Claim 46 that is an adenovirus vector.

50. (Original) The nucleic acid molecule of Claim 49 that is an adenoviral vector from a serotype C adenovirus.

51. (Currently Amended) The nucleic acid molecule of Claim 49 ~~or claim 50~~, wherein the heterologous nucleic acid encodes a therapeutic product.

52. (Currently Amended) The nucleic acid molecule of ~~any of claims 46-51~~ Claim 46 that is an early generation adenoviral vector, a gutless adenoviral vector or a replication-conditional adenoviral vector.

53. (Original) The nucleic acid molecule of Claim 52, wherein the replication-conditional adenoviral vector is an oncolytic adenoviral vector.

54. (Currently Amended) A cell, comprising the nucleic acid of ~~any of claims 46-53~~ Claim 46.

55-56. (Cancelled).

57. (Original) A cell of Claim 54 that is in a packaging cell line.

58. (Currently Amended) An adenovirus particle, comprising the modified fiber of ~~any of claims 1-45~~ Claim 1.

59. (Original) The adenovirus particle of Claim 58, wherein the capsid further comprises a penton modification.

60. (Currently Amended) The adenovirus particle of Claim 58 ~~or claim 59~~, wherein the modified fiber includes an N-terminal portion from a fiber of a serotype C Ad virus, wherein the N-terminal portion is sufficient to increase incorporation into the particle compared to in its absence.

61. (Currently Amended) The adenovirus particle of ~~any of claims 58-60~~ Claim 58, that comprises a modified serotype C genome, wherein the N-terminal portion of the modified fiber comprises at least the N-terminal 15,16 or 17 amino acids of a serotype C fiber.

62. (Original) The particle of Claim 61 wherein the serotype C virus is an Ad2 or Ad5 virus.

63. (Currently Amended) The adenoviral particle of ~~any of claims 58-62~~ Claim 58 that further comprises a targeting ligand in the capsid.

64. (Currently Amended) The adenovirus particle of ~~any of claims 58-63~~ Claim 58 further, comprising a heterologous nucleic acid in the genome thereof.

65. (Original) The adenovirus particle of Claim 64, wherein the heterologous nucleic acid encodes a therapeutically effective product.

66. (Currently Amended) The adenoviral particle of ~~any of claims 58-65~~ Claim 58 that includes a modification to the capsid whereby binding of the viral particle to HSP is altered compared to a particle that expresses an unmodified capsid.

67. (Original) The adenoviral particle of Claim 66, wherein the capsid modification that alters HSP binding is in the fiber.

68. (Currently Amended) An adenoviral particle of ~~any of claims 58-67~~

Claim 58, comprising a mutation in α - integrin-binding region of the capsid, whereby binding to the integrin is eliminated or reduced.

69. (Currently Amended) The adenoviral particle of ~~any of claims 58-68~~

Claim 58, wherein the fiber further comprises a modification in the fiber knob to further reduce any CAR binding.

70. (Original) The adenoviral particle of Claim 69, wherein the fiber knob modification is in the AB loop or CD loop.

71. (Original) The adenoviral particle of Claim 70, wherein the fiber knob modification is selected from the group consisting of K01 and K012.

72. (Currently Amended) A composition formulated for administration to a subject, comprising the adenovirus particle of ~~any of claims 58-74~~ Claim 58.

73. (Currently Amended) A method of detargeting an adenoviral vector, comprising reducing or eliminating the binding of an adenoviral particle to CAR by producing an adenoviral particle that expresses a modified fiber of ~~any of claims 1-45~~ Claim 1.

74. (Original) The method of Claim 73, wherein the modified fiber increases the binding to the particular cell type compared to the unmodified fiber.

75. (Original) The method of Claim 73, wherein the modified fiber comprises at least two modifications such that the binding to a selected cell type is increased relative to the unmodified fiber.

76. (Original) The method of Claim 75, wherein the second modification comprises the addition of a targeting ligand in the capsid of the adenoviral particle.

77. (Original) The method of Claim 75, wherein the second modification comprises the replacement of the fiber knob or a portion thereof.

78. (Currently Amended) method, comprising introducing an adenoviral particle of ~~any of claims 58-71~~ Claim 58 into cells ; and introducing the cells into a subject.

79. (Original) The method of Claim 78, wherein the cells are immune cells or fibroblasts.